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Morphometric Indicators of the Testis and Epididymis of Outbred Rats under Polypharmacy of Anti-Inflammatory Drugs and Correction with Pomegranate Seed Oil

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Abstract This article presents morphometric data of the testes of white outbred rats under polypharmacy with drugs that have an anti-inflammatory effect and after correction with pomegranate seed oil. The composition of the spermatogenic epithelium in each experimental group is described. The percentage of different types of seminiferous tubules before and after correction was determined.

Keywords Testes, Polypharmacy, Pomegranate seed oil

1. Introduction

Polypharmacy is when one or more medications are prescribed beyond clinical indications, resulting in adverse patient outcomes and failing to achieve the therapeutic goal. The scientists concluded that it should not be assumed that polypharmacy is always harmful and that clinical considerations on which medications were prescribed must be taken into account. However, the goal should be to ensure that patients receive only appropriate and targeted drug therapy to treat the disease [2].

An adverse drug effect is an injury resulting from drug use. An adverse drug reaction is an adverse drug effect that refers to harm caused by a drug at normal dosages. Adverse drug effects are estimated to account for 5% to 28% of acute geriatric hospitalizations. Preventable adverse drug events are among the serious consequences of inappropriate medication use. Classes of drugs commonly associated with preventable adverse drug events include cardiovascular drugs, anticoagulants, hypoglycemic agents, diuretics, and NSAIDs [5].

Each new drug prescribed increases the risk of side effects by 12-18% [1] and these iatrogenic accidents account for 5 to 25% of hospitalizations and 10% of emergency hospitalizations [3].

In addition, polypharmacy has been shown to be a prognostic factor in terms of length of hospital stay, mortality and readmissions [4]. Based on the above, we can conclude that the harm of polypharmacy on internal organs has not been studied, and its correction is considered one of the main dilemmas of modern medicine.

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The purpose of the study: to study the effect of anti-inflammatory drugs and correction with pomegranate seed oil on the morphometric indicators of the testis and epididymis of rats in an experiment.

2. Research Methods

The research was conducted in the scientific research laboratories of the Bukhara State Medical Institute and the Tashkent Medical Academy. In the experiment, the effect of several anti-inflammatory drugs and the result of correction were studied.

3-month-old white male rats (n=300) kept in standard vivarium conditions were selected for the experiment. To study polypharmacy, rats were given the following drugs: paracetamol 94.1 mg/kg + aspirin 31.3 mg/kg + ibuprofen 37.6 mg/kg + dexamethasone 0.6 mg/kg + hydroxychloroquine sulfate 40.7 mg/kg.

These drugs were administered intragastrically through a tube as a solution to each experimental group for 10 days. In last group, the experiment lasted relatively longer. That is, after the administration of drugs in the first 10 days, from the 11th to the 20th day, only pomegranate seed oil 10 mg/kg was administered for the purpose of correction. The control group received 0.5 ml of distilled water intragastrically instead of drugs.

At the end of the experiment, the rats were euthanized under light ether (chloroform) anesthesia on an empty stomach. Testes were isolated, weighed, fixed in 10% neutral formalin, dehydrated in increasing concentrations of alcohol, and embedded in paraffin. Sections 5-7 μm thick were prepared on a microtome, deparaffinized in xylene, and stained with hematoxylin and eosin.

NanoZoomer (REF C13140-21.S/N000198/HAMAMATSU PHOTONICS /431-3196 JAPAN) Hamamatsu (QuPath-0.4.0, NanoZoomer Digital Pathology Image) morphometric computer program were used for conducting morphometric examinations.

The research materials were statistically processed.

3. Research Results and Conclusions

Morphometric studies showed that the thickness of the membrane of testes of other experimental groups was not significantly different from that of experimental animals in the control group. However, when compared with the results of the control group, the number of convoluted seminiferous tubules, average diameter and volume of spermatogenic epithelia in the rats of the experimental group were lower to 26.8% compared to the control group, for example, 20.5% in the 1st group, 19.8% in the 2nd group, 17.6% in 3 groups and 16.3% in 4 groups, on the contrary, it was noted that the interstitial tissue area increased by 20.5% in all groups compared to the control group (Table 1).

The changes in the size of the convoluted seminiferous tubules are one of the important quantitative indicators indicating a decrease in the process of spermatogenesis in the testicles.

According to the degree of extrusion of the spermatogenic epithelium, convoluted seminiferous tubules are divided into 5 types. Convoluted seminiferous tubules of the I type are formed by tubules with a regular structure, containing cells at different stages of differentiation, and these cells are located in accordance with the stages of the spermatogenesis process. Type II convoluted seminiferous tubules with signs of slight damage to the structure of the spermatogenic epithelium, type III with clearly expressed violations in the spermatogenic epithelium, type IV - convoluted seminiferous tubules that are empty, and type V - seminiferous tubules in which the process of spermatogenesis is not completed, but without signs of degeneration of germ cells.

The parameters of convoluted seminiferous tubules determined according to the degree of extrusion in the testes of experimental rats are presented in Table 2.

As can be seen from the table, the percentage of type I-II tubes decreased by 53.57% due to the formation of type III-IV-V seminiferous tubules in the testes of rats of the experimental group. It should be noted that in the testes of experimental animals in the control group there were no convoluted seminiferous tubules of type III-IV. At the same time, it was noted that the percentage of tubules actively producing spermatozoa decreased in the experimental group compared to the control group according to the indicators presented in the table below.

Thus, polypharmacy in rats caused by the combined use of different medicinal substances in groups leads to disruption of the generative function of the convoluted tubules in the testes of rats. This situation manifests itself in the form of the appearance of abnormal III-IV-V type convoluted tubules in testicles, and the occurrence of atrophic and destructive changes in them. All of the above indicates that the spermatogenesis process in the rats of the experimental group and the number of mature germ cells are reduced (Figures 1, 2).

Table 1. Morphometric parameters of testes of rats in control and experimental groups (M±m)

Indicators	Groups					
	Control group	1-group	2-group	3-group	4-group	After correction
The thickness of the testes membrane, μm	34,9±1,65	33,6±0,57	31,1±0,21	28,8±0,16	26,5±0,11	31.1,9±1,05
The number of convoluted testes tubes in one field of view, pcs	33,8±1,58	24,4±1,32*	21,1±1,32*	20,1±1,05*	18,3±1,01*	30,8±1,22
Diameter of convoluted seminiferous tubules, μm	224,3±10,71	216,8±5,85*	202,8±4,27*	197,6±3,62*	184,8±5,45*	220,3±8,51
Thickness of spermatogenic epithelium, μm	35,7±1,67	33,6±1,16*	31,3±1,32*	30,1±1,05*	27,8±1,13*	34,6±1,27
Interstitial tissue area, μm^2	1226,14±42,1	1358,0±54,1*	1453,0±56,2*	1536,0±41,8*	1656,0±46,1*	1311,14±26,2
Spermatogenesis index	3,7±0,14	3,3±0,13	3,0±0,11	2,8±0,13	2,2±0,08	3,5±0,25

Note: *-differences are reliable compared to control group values, P<0.05.

Table 2. Types of convoluted seminiferous tubules in rat testis (M±m)

Group	Types of convoluted tubes (%)				
	I	II	III	IV	V
Control	86,6±3,82	13,4±0,63	-	-	-
1-group	68,6±1,78*	20,1±1,14*	6,1±0,54*	2,3±0,16*	2,9±0,16*
2-group	58,6±1,58*	24,3±1,08*	9,1±0,54*	3,6±0,16*	4,4±0,16*
3-group	52,3±1,01*	26,3±1,08*	12,1±0,54*	4,2±0,16*	5,1±0,16*
4-group	46,4±2,58*	32,1±1,07*	14,1±0,54*	4,8±0,16*	2,61±0,16*
After correction	79,3±1,15*	15,1±0,71*	2,1±0,52*	1,6±0,11*	1,9±0,08*

Note: *-differences are reliable compared to control group values, P<0.05.

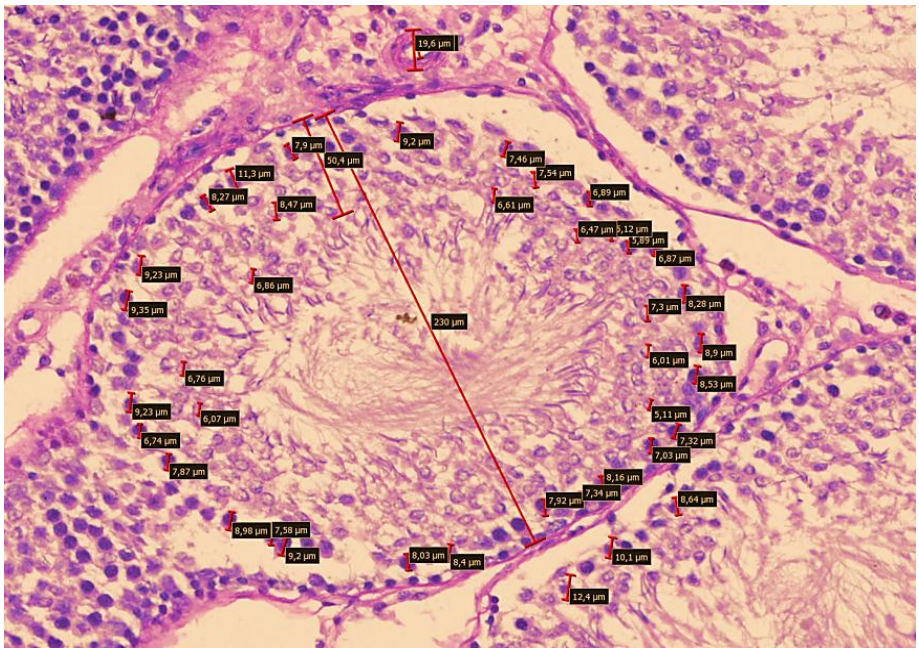

Figure 1. Sizes of the convoluted tubule of control rats obtained from morphometric computer software

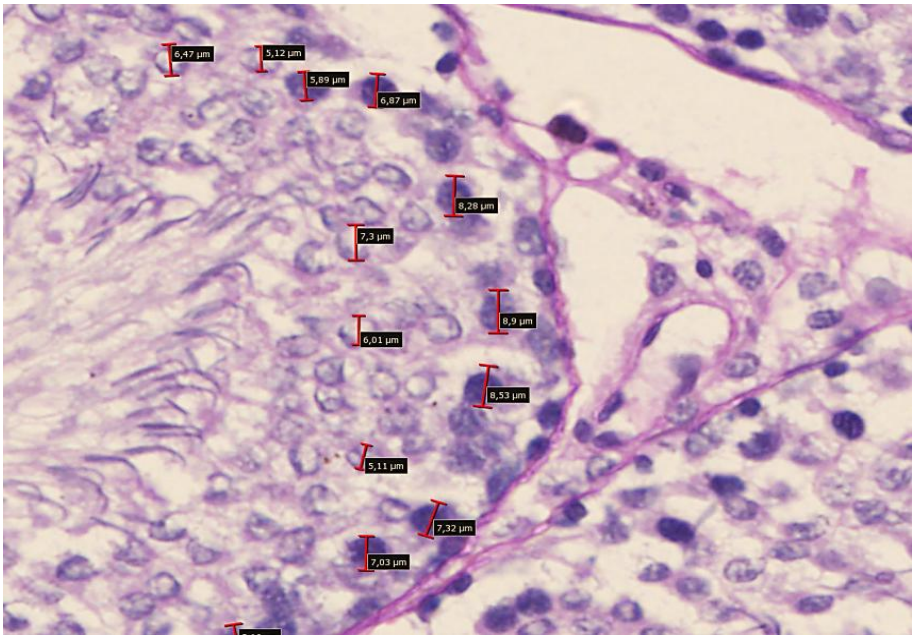

Figure 2. Sizes obtained from the morphometric computer program of the convoluted tubes of rats of the experimental group in polypharmacy

Table 3. Cellular composition of rat seminiferous tubules and interstitial tissue, (M±m)

Group	Cells in the wall of convoluted seminiferous tubules (in absolute numbers)				Leydig cells (in absolute numbers)
	Spermatogonia	Spermatocytes	Spermatids	Sertoli cells	
Control	49,2±2,23	94,6±4,42	144,8±6,58	26,4±1,17	34,7 ±1,63
1-group	39,3±2,01*	80,4±1,78*	120,1±4,16*	20,3±1,08*	21,23±0,27*
2-group	32,1±1,76*	72,2±1,08*	112,4±3,06*	16,8±1,23*	18,01±0,16*
3-group	29,5±1,16*	61,2±1,18*	92,4±3,01*	14,1±1,01*	14,16±0,08*
4-group	22,3±2,02*	56,6±1,12*	82,4±2,06*	12,01±1,09*	9,12±0,05*
After correction	44,3±1,65*	86,3±2,72*	136,3±5,16*	23,7±1,02*	30,12±1,11*

Note: *-differences are reliable compared to control group values, P<0.05.

To evaluate the composition of the spermatogenic epithelium, the quantitative indicators of germ cells and Sertoli cells located in the convoluted seminiferous tubules in the testes of rats in the control and experimental groups were studied (Table 3).

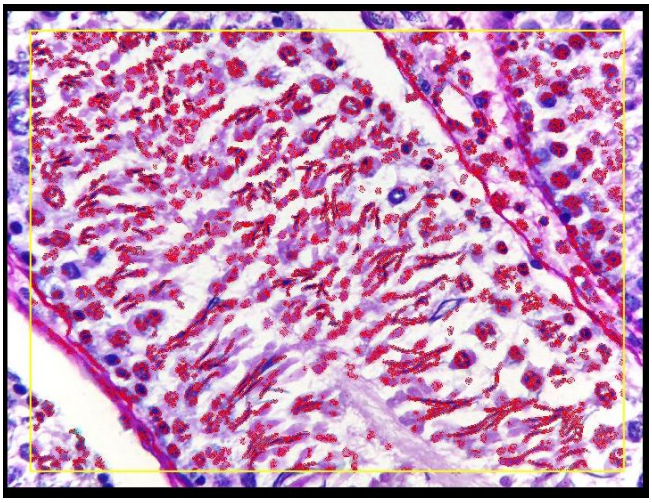

Figure 3. Graphical representation of the number of cells determined by morphometric computer software of testicular wall epithelial cells of rats treated with pomegranate seed oil after polypharmacy

The obtained results showed that polypharmacy in rats causes a change in the quantitative composition of convoluted seminiferous tubules and interstitial Leydig cells in the testes of rats in decreasing order. It was found that the number of all types of spermatogenic epithelial cells - spermatogonia, spermatocytes and spermatids in the rats of the experimental group decreased accordingly compared to the indicators of the control group. This, in turn, led to a decrease in the total number of spermatogenic cells, Sertoli and Leydig cells. The number of Sertoli cells also showed a decreasing trend and was found to be significantly reduced compared to the control group. Accordingly, it was found that the spermatogenesis index was from 34.9±1.65 in the control group to 3.7±0.14 in the experimental group, which decreased by 10 times compared to the control group and was 10.6%. It was also found that the number of interstitial Leydig cells significantly decreased in most of the experimental groups in polypharmacy. It was found that the number of these cells decreased to a total of 26.28% compared to the control group. After treatment with pomegranate seed oil, the number of Sertoli and Leydig cells increased and approached normal values (Figure 3).

Summarizing the obtained morphometric indicators, significant structural and quantitative changes in the structures of the testicles develop in polypharmacy in rats under experimental conditions. These changes involved Leydig cells as well as the maturing germ cells and Sertoli cells in the spermatogenic epithelium. But correction with pomegranate seed oil showed positive changes in all the structures of the testicles and epididymis.

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